



Risk of neuropsychiatric disorders in offspring of COVID-19-infected pregnant women and nutritional intervention

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After the detection of the novel coronavirus disease (COVID-19) in December 2019 in Wuhan city, Hubei province, China, individuals infected with COVID-19 are markedly increasing in the world. On March 11, 2020, the World Health Organization declares COVID-19 outbreak a pandemic. The ongoing COVID-19 outbreak is a public health emergency worldwide. However, there are currently no approved drugs for COVID-19 although clinical trials of a number of candidates are underway [1].

On February 12, 2020, Chen et al. [2] reported the clinical characteristics of COVID-19 in nine pregnant women with laboratory-confirmed COVID-19 pneumonia and intrauterine vertical transmission potential of COVID-19 at the Zhongnan Hospital of Wuhan University, China. All patients underwent caesarean sections in the third trimester. The range of gestational weeks at admission was 36 weeks to 39 weeks plus 4 days. Gestational age of the four patients was before 37 weeks. Nine livebirths were recorded without fetal death, neonatal death, or neonatal asphyxia observed in the newborn babies. Thus, there is currently no evidence showing intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in the late stages of pregnancy [2]. However, further study using a large sample size is needed.

Epidemiological studies suggest that maternal immune activation (MIA) plays a role in the etiology of neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia. Maternal infectious pathogens and inflammation have been associated with these neuropsychiatric disorders. C-reactive protein (CRP) is a well-established blood biomarker of inflammation from both infectious and

noninfectious exposures. Among the nine pregnant women infected with COVID-19, six displayed elevated concentration (> 10 mg/L) of CRP, which indicated severe inflammation [2].

A national birth study in Finland suggested that high levels of CRP during pregnancy are significantly associated with ASD in offspring [3]. A significant elevated risk of 43% is observed in maternal early gestational CRP levels in the highest quintile (> 58.4 mg/L) compared with the lowest quintile (1.0–9.2 mg/L) [3]. Furthermore, a meta-analysis showed that higher maternal CRP levels were significantly associated with schizophrenia in offspring (odds ratio 1.31, 95% confidence interval (CI) 1.11–1.55, standard mean differences = 0.15, 95% CI 0.06–0.24, $P < 0.01$) [4]. In contrast, there is still a lot of debate on the relationship of CRP levels in pregnancy and neuropsychiatric disorders in offspring. It is widely recognized that MIA, such as elevated maternal CRP, may play a significant role in the development of these neuropsychiatric disorders in offspring although further study is needed.

There are increasing interests in the potential benefit of early intervention by safe anti-inflammatory nutrition since MIA including maternal infection which plays a crucial role in the development of neuropsychiatric disorders [5, 6]. Consumption of broccoli is known to bring a number of health benefits, including reducing the risk of cancer and inflammatory diseases. Sulforaphane is an organosulfur compound derived from a glucosinolate precursor glucoraphanin, which is found in cruciferous vegetables such as broccoli sprout (Fig. 1) [5, 6]. Glucoraphanin is metabolized to sulforaphane by the plant enzyme myrosinase, active during chewing, or gut microbiota. Sulforaphane is well recognized to have potent anti-inflammatory and anti-oxidant effects [5, 6].

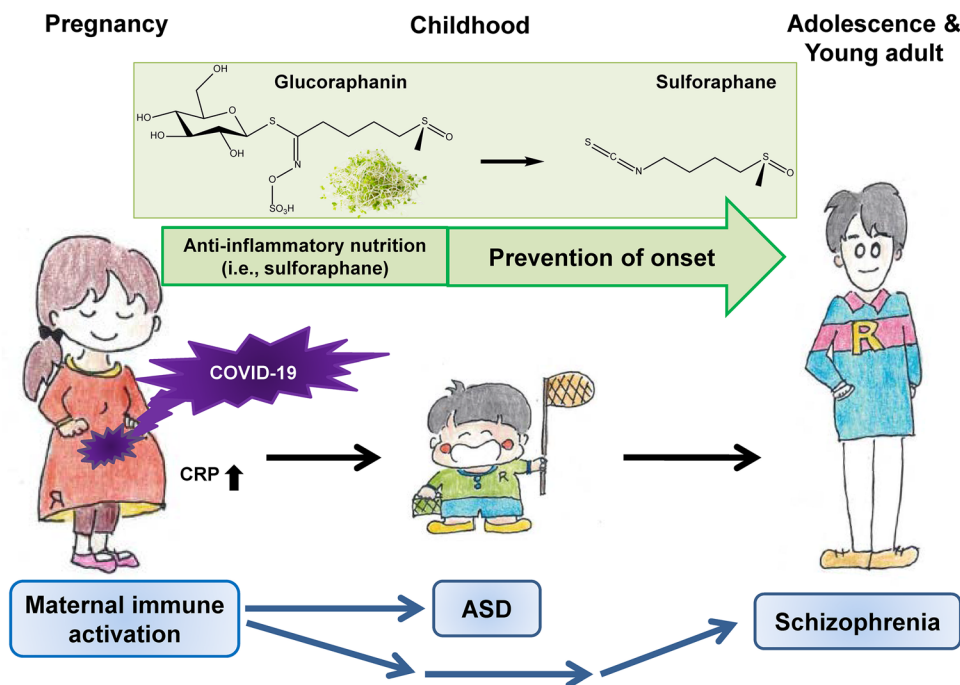
Previously, we reported that dietary intake of glucoraphanin food pellet during juvenile and adolescence could attenuate the development of schizophrenia-like behaviors in mice after repeated administration of phencyclidine [7]. In rodents, MIA using polyriboinosinic-polyribocytidylic

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Fig. 1 Potential intervention by dietary intake of anti-inflammatory nutrition on the development of neuropsychiatric disorders in offspring after maternal infection of COVID-19. Maternal immune activation (MIA) by COVID-19 infection causes inflammatory events in pregnant women with COVID-19, resulting in higher CRP levels in blood. Given the role of MIA in neuropsychiatric disorders such as ASD and schizophrenia, follow-up investigation of pregnant women infected with COVID-19 and their children is needed. For example, dietary intake of anti-inflammatory nutrition (i.e., sulforaphane and its precursor glucoraphanin) may reduce the risk of neuropsychiatric disorders in offspring after maternal infection of COVID-19



acid [poly (I:C)], a toll-like receptor 3 agonist, produces ASD-like and schizophrenia-like behaviors in offspring. Therefore, MIA model using poly (I:C) has been widely used as an animal model for neurodevelopmental disorders. We reported that dietary intake of glucoraphanin food pellet during juvenile and adolescence could attenuate the development of schizophrenia-like behavior in adult offspring after MIA [8]. Interestingly, dietary intake of glucoraphanin food pellet during pregnancy and lactation could attenuate the development of ASD-like and schizophrenia-like behaviors in juvenile and adult offspring after MIA [9]. Interestingly, Singh et al. [10] demonstrated that dietary intake of sulforaphane caused substantial declines of Aberrant Behavior Checklist and Social Responsiveness Scale scores in young men ($n = 29$) with ASD. A subsequent follow-up study showed that many parents and caregivers had positive effects of sulforaphane, both during the intervention study and the ensuing three years [11]. Beneficial effects of sulforaphane are of great interest although future studies using a large sample size should address its potential benefits for the prenatal prevention of ASD as well as for the delay in the early prevention of young children with ASD [10, 11]. Collectively, it is likely that dietary intake of glucoraphanin food pellet could produce potent prophylactic effects in the development of neuropsychiatric disorders in rodents [6, 7].

In conclusion, the number of pregnant women infected with COVID-19 is expected to increase in the world [12]. It is very important to prevent the infection of COVID-19 in women during pregnancy. Given the risk of MIA in neuropsychiatric disorders such as ASD and schizophrenia, follow-up investigations of pregnant women infected with

COVID-19 and their children will be necessary to ascertain the risk of neuropsychiatric disorders, such as ASD and schizophrenia, in offspring. Furthermore, dietary intake of anti-inflammatory nutrition (i.e., sulforaphane and its precursor glucoraphanin) in pregnant women with COVID-19 infection and their children may reduce the risk of neuropsychiatric disorders such as ASD and schizophrenia (Fig. 1). Future randomized, double-blind, placebo-control study is needed to ascertain whether supplementation of sulforaphane or its precursor glucoraphanin in pregnant women with COVID-19 infection or their children could reduce the onset of neuropsychiatric disorders.

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